MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 14, 2005

FROM: Kathleen M. Phelan, R.Ph., Safety Evaluator
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THROUGH: Mark Avigan, M.D., Director
Div. of Drug Risk Evaluation, HFD-430

TO: Solomon Iyasu, MD, MPH., Team Leader
Div. of Pediatric Drug Development, HFD-960
Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review, PID# D040058
Drug : Concerta (OROS methylphenidate) NDA#: N21-121
Pediatric Exclusivity Approval Date: December 4, 2003

Executive Summary

Concerta is an extended-release formulation of methylphenidate hydrochloride using OROS® tablet technology. Concerta was approved on August 1, 2000, for treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients aged 6 to 12 years. On October 21, 2004, Concerta's indication was expanded to include adolescent patients aged 13 to 17 years. Thus, Concerta labeling is based on information gained in studies and experience with children. This 1-year post-pediatric exclusivity review finds the post-marketing adverse event profile to correspond with Concerta labeling in most areas. The areas of possibly insufficient labeling are psychiatric adverse events, which are presented in labeling as exacerbations of pre-existing conditions or as being reported with methylphenidate products other than Concerta, and cardiovascular adverse events. Cardiovascular adverse events, such as increased blood pressure and cerebrovascular accident, with drugs used to treat ADHD are currently under FDA review. I recommend an AERS review of psychiatric adverse events; although the events are labeled, the context in which they occur may require updating.

AERS Search Results: Concerta

AERS Search includes all sources - U.S. & foreign

A. From marketing approval date (August 1, 2000) through AERS data cut-off date (January 4, 2005).

1. Raw counts of reports: Table 1 (parentheses denote U.S. origin report counts)

	All reports (US)	Serious (US)	Death (US)
All ages	936 (711)	862 (639)	52 (47)
Adults (≥17)	162 (136)	152 (126)	35 (32)
Ped. (0-16)	642 (479)	599 (438)	16 (14)

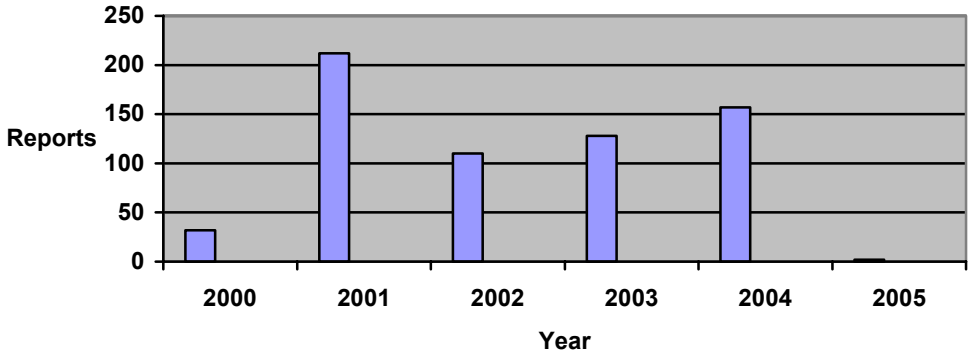

Figure 1: Reporting trend for pediatric reports from Concerta approval date (August 1, 2000)

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups. Events not described in the label are underlined.

All ages: drug ineffective (85), pharmaceutical product complaint (77), insomnia (64), headache (63), aggression (52), abnormal behavior (48), nausea (44), vomiting (44), agitation (43), condition aggravated (43), abdominal pain (39), drug effect decreased (38), medication error (38), anorexia (35), hallucination (33), anxiety (31), convulsion (30), depression (29), suicidal ideation (29), drug interaction (28)

Adults: nausea (19), agitation (17), completed suicide (14), insomnia (14), pharmaceutical product complaint (12), somnolence (12), intentional overdose (10), coma (9), convulsion (9), drug ineffective (9), vomiting (9), tremor (8), back pain (7), confusional state (7), depressed level of consciousness (7), diarrhea (7), disorientation (7), dizziness (7), drug withdrawal syndrome (7), heart rate increased (7)

Pediatric: drug ineffective (54), headache (52), aggression (45), insomnia (44), pharmaceutical product complaint (42), abnormal behavior (41), condition aggravated (36), abdominal pain (35), anorexia (32), vomiting (31), hallucination (30), anxiety (26), drug effect decreased (25), agitation (24), nausea (24), chest pain (23), depression (21), muscle twitching (21), suicidal ideation (20), drug interaction (19)

B. From Pediatric Exclusivity approval date (December 4, 2003) through AERS data cut-off date (January 4, 2005):

1. Raw counts of reports: Table 2 (parentheses denote U.S. origin report counts)

	All reports (US)	Serious (US)	Death (US)
All ages	265 (144)	243 (123)	13 (13)
Adults (≥17)	56 (46)	51 (41)	10 (10)
Ped. (0-16)	164 (77)	149 (63)	3 (3)*

* Two deaths occurred in adults, one death was attributable to cocaine use.

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups. Events not described in the label are underlined.

All ages: insomnia (20), nausea (17), heart rate increased (16), abnormal behavior (15), aggression (15), suicidal ideation (15), agitation (13), medication error (13), pharmaceutical product complaint (13), drug ineffective (12), headache (12), vomiting (12), chest pain (11), convulsion (11), depression (10), drug interaction (9), abdominal pain (8), anxiety (8), blood pressure increased (8), overdose (8)

Adults: nausea (10), agitation (9), insomnia (8), heart rate increased (7), completed suicide (6), pharmaceutical product complaint (5), vomiting (5), convulsion (4), somnolence (4), therapeutic agent toxicity (4), treatment noncompliance (4), asthenia (3), chest discomfort (3), diarrhea (3), disorientation (3), disturbance in attention (3), drug interaction (3), grand mal convulsion (3), mental status changes (3), multiple drug overdose (3)

Pediatric: aggression (13), abnormal behavior (11), chest pain (11), insomnia (11), headache (10), suicidal ideation (10), medication error (9), abdominal pain (8), anorexia (7), anxiety (7), depression (7), drug ineffective (7), nausea (7), vomiting (7), blood pressure increased (6), drug interaction (6), visual hallucination (6), heart rate increased (6), overdose (6), convulsion (5)

Postmarketing hands-on review of all pediatric adverse event reports from all sources received during the first year after Concerta received pediatric market exclusivity.

Of 164 reports retrieved by this search, 2 involve adults, 5 are duplicate reports, 14 involve non-Concerta methylphenidate products, and 8 specify no adverse effects (see Attachment 3). The remaining 135 cases include 19 cases that are strongly confounded (see Attachment 1) and 116 cases reporting specific adverse events without strongly confounding information (see Attachment 2). These 135 reports are described below.

A. Characteristics of pediatric reports (N=135)

Origin: foreign – 77, U.S. – 58

Gender: female - 26, male – 108, unknown - 1

Standard AERS age breakdown:

0-<1 mo.	0
1 mo.- <2 yrs	0
2-5 yrs	1
6-11 yrs	82
12-16 yrs	52

Outcomes selected on MedWatch form[1]: deaths - 1, hospitalizations - 39, life threatening - 5, required intervention - 1, medically important – 69, other - 26, disability - 5, no outcome selected - 7

Indications or clinical conditions for which Concerta was used: ADHD/hyperactivity disorder – 108, disturbance in attention – 2, learning disability – 1, oppositional defiant disorder – 1, pervasive developmental disorder – 1, Tourette's disorder – 1, unknown – 21

Prescribed dosages: range 18 to 108 mg per day, median 36 mg per day, mean 39 mg per day. Dosage was unknown or not reported in 17 cases. Five patients, (including one who took an acute overdose) received dosages greater than the labeled maximum of 72 mg per day for adolescents.

B. Comments on labeling status of the top 20 adverse events in pediatric patients and comparison to adult adverse event profile.

All but two of the unlabeled events reported most frequently in pediatric patients are psychiatric events. These are aggression, agitation, abnormal behavior, anxiety, depression, visual hallucination, and suicidal ideation. Labeling states, in the *Contraindications* section, under *Agitation*, "Concerta is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms." Also, labeling states, in the *Warnings* section, under *Psychosis*, "Clinical experience suggests that in psychotic patients, administration of methylphenidate may exacerbate symptoms of behavior disturbance and thought disorder." Also mentioned in the *Adverse Reactions* section of labeling are sadness, nervousness, and emotional lability. In the *Adverse Reactions* section under Adverse Events with Other Methylphenidate HCl Products, transient depressed mood and toxic psychosis are listed. Therefore, Concerta labeling does include these psychiatric adverse events but conveys that they are not serious or that they are exacerbations of pre-existing conditions, not new-onset, or that they have not been reported at therapeutic doses, or specifically with Concerta. The adult profile also includes some psychiatric events, specifically, agitation and completed suicide.

[1] A report may have more than one outcome selected.

The remaining unlabeled events reported in pediatric patients are chest pain and medication error. Medication errors are never an acceptable risk, or labeled (expected) adverse effect of any medication. Concerta labeling does not specify chest pain, but tachycardia, angina, and cardiac arrhythmia, which may be associated with chest pain, are labeled in the *Adverse Reactions* section under Adverse Events with Other Methylphenidate HCl Products. The adult adverse event profile includes chest discomfort.
Overall, the pediatric and adult adverse event profiles are similar.

C. Comments and analysis of unlabeled adverse events seen in pediatric population.

Psychiatric adverse events represent the main area of unlabeled adverse events. Concerta labeling describes exacerbation of psychiatric symptoms in children with pre-existing psychiatric illness and states that toxic psychosis has occurred with other methylphenidate dosage forms. However, specific, newly-emergent psychiatric adverse events occurring in children receiving Concerta at therapeutic doses are not described in labeling. Among 36 reports of psychiatric adverse events, 6 report histories of psychiatric illness other than that being treated with Concerta, 3 deny history of other psychiatric illness, and 27 neither report nor deny other psychiatric illness. The psychiatric histories reported in six cases are post-traumatic stress disorder, post-traumatic stress disorder and violent tendencies, schizoaffective disorder, Asperger's syndrome, anxiety and depression, and unspecified behavioral problems. In children presenting with behavioral problems that warrant treatment with Concerta, previously unrecognized psychiatric illnesses must be considered. When such illnesses exist, use of a stimulant may exacerbate symptoms and reveal them for the first time. Under this scenario, the labeled statements that psychoses and agitation may be aggravated are accurate. However, because psychiatric adverse events have occurred during Concerta therapy in children with no other diagnosed psychiatric illnesses, further review of psychiatric events, such as visual hallucinations and aggression, may determine if labeling should be changed to state that the events have been seen without specifying that they represent exacerbation of pre-existing conditions.

The nine reports of medication error comprise three cases in which the wrong drug was dispensed but not ingested; two cases in which no adverse event occurred after drying and snorting tablet contents in one case and after accidentally taking two doses in one day in the other case; and one case each of adverse events occurring after accidentally taking two doses in one morning, after holding the tablet in the mouth all day, after taking a dose in the afternoon rather than in the morning as usual, and after swallowing the tablet rather than receiving it through the gastrostomy tube. If evaluation of the cases associated with medication error is desired, the Division of Medication Errors & Technical Support in the Office of Drug Safety should be consulted.

The 11 reports of chest pain include one duplicate and one case of chest pain starting before Concerta therapy was initiated. Thus, this search found nine cases of chest pain temporal to Concerta use. One of the nine cases was confounded by lithium

toxicity following an increase in lithium dosage, Concerta labeling includes tachycardia, changes in blood pressure, angina, and cardiac arrhythmia in the *Adverse Reactions* section as events reported with other methylphenidate products. Seven of the nine cases of chest pain in this review include other adverse events possibly related to cardiac effects such as dyspnea, increased blood pressure, EKG abnormalities, and tachycardia. Chest pain may not always represent cardiac adverse effects. However, if chest pain were a labeled event, investigation for possible underlying cardiac effects might not be performed when chest pain occurs. Therefore, it may be preferable to leave chest pain out of Concerta labeling. Currently, FDA is reviewing cardiovascular effects of the drugs used to treat ADHD to determine what action to take.

D. Comments and analysis of labeled events that are uniquely reported in pediatric patients but are not reported in adult population.

From the top 20 reported events in the first year after pediatric exclusivity was granted, labeled events uniquely reported in pediatric patients are headache, abdominal pain, anorexia, and blood pressure increased. Adults do report nausea, vomiting, and diarrhea, which suggest similar gastrointestinal effects. Also, adults report increased heart rate and chest discomfort, which suggest similar cardiovascular effects. Thus, the uniquely reported terms do not seem to indicate categorically different effects in pediatric and adult patients.

E. Comments on increased reporting frequency of expected events.

None of the top 20 expected adverse events were reported at substantially greater frequency in the first year following pediatric exclusivity than during the previous years of Concerta marketing.

F. Reports of death[2].

The AERS search retrieved three reports of death during the 1-year period following the granting of pediatric exclusivity. Two deaths occurred in adults and one death was confounded by cocaine. This death by cardiac arrest occurred 1 week after Concerta was discontinued and cocaine was found on the 16-year-old male's clothing.

G. Summary of the pediatric adverse event profile during the 1-year period following the granting of pediatric exclusivity for events such as maternal exposure, overdose or multiple drug usage.

The pediatric adverse event profile in the first year after pediatric exclusivity was granted included one maternal exposure in a 15-year-old girl who spontaneously aborted. There was a history of unspecified fetal abnormality in her family. One patient was 5 years old, but the remaining 134 patients were 6 years old or older, in keeping with Concerta labeling. Five patients were prescribed 108 mg per day, but

[2] NOTE: There was one report (ISR# 4267018-3) of a non-fatal sudden cardiac death occurring in a 13-yo male with coarctation of the aorta and two mitral valve replacements. He was on the heart transplant list.

the remaining patients whose prescribed doses were reported received 72 mg per day or less, in keeping with Concerta labeling. Six cases of overdose comprise three accidental administrations of two or three doses in one day, one purposeful ingestion of four doses in one day for increased therapeutic effect, one purposeful ingestion of three tablets prescribed to a classmate, and one purposeful ingestion of 20 tablets. Adverse events in three cases included increased heart rate, increased blood pressure, posturing, hyperventilation, and dilated pupils. Total doses ingested are unknown in these three cases. Three overdose cases reported overdoses of 108, 144, and 162 mg (see Attachment 3). No adverse effects were reported in these three cases and they are not included in the 135 cases described in most of this review. All overdose patients recovered. Intentional misuse of Concerta was reported in four cases, including three overdoses. Two misuses appeared to be for recreation, one was for increased therapeutic effect, and one appeared to be for intentional self-harm. There were no unexpected adverse events. However, many psychiatric adverse events were reported in children with no reported psychiatric illness other than that being treated with Concerta at labeled dosages. Concerta labeling presents a different impression of psychiatric adverse events in that labeling describes exacerbations of pre-existing psychoses and agitation, but not new-onset psychosis or aggression, and includes toxic psychosis under adverse events with other methylphenidate products.

Summary

Concerta is an extended-release formulation of methylphenidate hydrochloride using OROS® tablet technology. Concerta was approved on August 1, 2000, for treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients aged 6 to 12 years. On October 21, 2004, Concerta's indication was expanded to include adolescent patients aged 13 to 17 years. Thus, Concerta labeling is based on information gained in studies and experience with children. This 1-year post-pediatric exclusivity review finds the post-marketing adverse event profile to correspond with Concerta labeling in most areas. The only areas of possibly insufficient labeling are psychiatric adverse events, which are presented in labeling as exacerbations of pre-existing conditions or as being reported with methylphenidate products other than Concerta, and cardiovascular adverse events. Cardiovascular adverse events, such as hypertension and cerebrovascular accident, with drugs used to treat ADHD are currently under FDA review. I recommend an AERS review of psychiatric adverse events; although the events are labeled, the context in which they occur may require updating.

S*igned June 14, 2005*
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Safety Evaluator

Concur:

Signed June 14, 2005
Cindy Kortepeter, Pharm. D.
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Limitations of the Adverse Event Reporting System (AERS)

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

Attachments:

1. Cases that are strongly confounded (N=19)
2. Cases of adverse events that do not include strongly confounding information (N=116)
3. Cases in which no adverse event was reported (N=8)

Attachment 1: Cases that are strongly confounded (N=19)

ISR#	Age (yrs)	Gender	Summary
4449142-5	10	Male	Lithium toxicity after increased lithium dosage
4256552-8	16	Male	Cardiac arrest 1 week after Concerta discontinued. Cocaine found at scene
4404445-5	15	Male	Arrested for public intoxication after ingesting alcohol
4485747-3	13	Male	Diabetes Mellitus type 1 diagnosed and treated with insulin during ongoing Concerta therapy. Family history of DM type 1
4311943-1	12	Male	Increased creatine phosphokinase with pre-existing myopathy. CPK subsided during ongoing Concerta therapy
4400052-9	12	Male	Gynecomastia with risperidone use. Risperdal label has precaution about increased prolactin and it's effects
4369044-2	12	Male	Hallucinations surrounding sleep for a few days after surgery with general anesthesia and during codeine and cyclizine use. Cyclizine is labeled for hallucinations.
4323752-8	7	Female	Hallucinations resolved with discontinuation of citalopram and ongoing Concerta therapy
4431336-6	14	Male	Infectious mononucleosis treated with antibiotics
4276414-x	11	Male	Chest pain beginning before Concerta therapy
4285495-9	14	Male	Hypotension and syncope episodes continued after Concerta discontinued and resolved after Concerta resumed
4363198-x	15	Male	Hematuria and back pain after 13 months Concerta therapy resolved with continued Concerta
4489174-4	13	Male	Leukopenia and neutropenia after 13 days Concerta therapy resolved with continued Concerta
4338460-7	13	Male	Increased alanine transaminase and lip cyanosis after 6.5 months Concerta therapy resolved with continued Concerta
4424339-9	16	Male	Decreased visual acuity 1 month after Concerta discontinued
4267018-3	13	Male	Sudden cardiac death and pacemaker insertion during Concerta therapy in child awaiting transplant due to congestive cardiomyopathy
4388089-x	11	Male	Self-injury, suicidal ideation, social withdrawal soon after sertraline added to Concerta therapy of 3 years duration
4415719-6	11	Male	Homicidal and suicidal ideation 2 weeks after initiating sertraline. Timing of Concerta therapy unknown
4534208-1	6	Male	Violent behavior after abruptly discontinuing Concerta. History of violent behavior before Concerta therapy

Attachment 2: Cases of adverse events that do not include strongly confounding information (N=116)

ISR#	Age (yrs)	Gender	Summary
Overdose/Abuse (N=3)			
4499120-5	16	Female	Took 3 tablets of methylphenidate that belonged to a classmate and experienced increased heart rate
4265397-4	11	Female	Accidentally received 2 doses in one morning and experienced increased blood pressure, posturing, hyperventilation, and crying
4355365-6	16	Male	Took 20 Concerta tablets and experienced logorrhea, insomnia, blurred vision, oral hypoesthesia, agitation, twitching, and dilated pupils
Lack of Effect (N=3)			
4527317-4	11	Male	Lack of effect with 7 months Concerta
4383922-x	12	Male	Lack of effect with 6 months Concerta. Resolved with dosage adjustment
4545209-1	11	Male	Lack of effect with 6.5 months Concerta
Psychiatric Adverse Events (N=36)			
4516223-7	12	Male	Anxiety, violent behavior, aggression after about 1 month Concerta. Concerta discontinued, events resolved
4290062-7	12	Female	Depression, suicidal ideation after 1 month Concerta. Concerta discontinued, events resolved
4334699-5	12	Female	Trichillomania, self-injurious behavior, suicidal ideation soon after Concerta added to paroxetine. Both drugs discontinued, events resolved
4395831-0	10	Male	Suicide attempt and suicidal ideation 2-3 weeks after starting Concerta. Concerta discontinued, events resolved
4297427-8	9	Female	Suicidal ideation during Concerta. Time to onset and outcome unknown.
4343732-5	9	Male	Suicidal ideation, sadness, anxiety, fearfulness, crying with first dose Concerta. Concerta discontinued, events resolved
4414939-4	9	Male	Choreoathetoid movements, euphoria, insomnia after 4 days Concerta. Concerta discontinued, events ongoing 2 ½ weeks later

ISR#	Age (yrs)	Gender	Summary
4530562-5	9	Male	Threaten suicide and described as "danger to himself and others" after 2 years Concerta and fluoxetine. Both drugs discontinued, events ongoing 2 days later
4516214-6	8	Male	Anorexia, insomnia, and physical aggressiveness after more than 2 years Concerta. Concerta and events continue
4543940-5	7	Female	Psychotic behavior after first dose Concerta. Concerta discontinued, event resolved
4297425-4	6	Male	Hallucinations and headache after about 1 month Concerta. Concerta and events continue
4500602-8	6	Male	Increased activity and increased violent behavior soon after start Concerta. Concerta discontinued, other treatments given, events improved
4290188-8	6	Male	Increased anxiety and pica less than 1 month after start Concerta. Concerta discontinued, events improved
4270799-6	6	Male	Abnormal behavior (licking table) after 1 day Concerta. Concerta ongoing, event resolved
4315477-x	6	Male	Unspecified change in behavior after 4 months Concerta. Outcome unknown
4383170-3	6	Male	Increased irritability, increased waking, possible hallucinations during Concerta. Concerta discontinued, events improved
4516221-3	6	Female	Violent behavior and aggression soon after increase dosage after about 2 years Concerta. Concerta and events ongoing
4416161-4	6	Female	Visual hallucinations 4 days after dosage increase after 4 months interrupted Concerta. Concerta discontinued, event resolved
4334819-2	14	Male	Psychosis and suicidal gesture during Concerta. Onset and outcome unknown
4370915-1	11	Male	Hallucinations and abnormal thinking after 6 weeks Concerta. Concerta discontinued, schizophrenic psychosis diagnosed, olanzapine started, events ongoing
4437824-0	15	Female	Phobia after about 3 months Concerta. Concerta dosage decreased, event resolved
4337854-3	14	Male	Aggression, urticaria, decreased appetite after 2 days Concerta. Concerta discontinued, events resolved
4357504-x	12	Male	Psychosis and aggression after 2 weeks Concerta. Concerta discontinued, events resolved
4338458-9	8	Male	Hallucinations, insomnia, bad dreams after 1 day Concerta. Continue for 1 week during Concerta. Concerta discontinued, events resolved
4404757-5	8	Male	Anxiety, social withdrawal, listlessness, fearfulness, excessive rumination after 1 ½ months Concerta. Concerta discontinued, events resolved

ISR#	Age (yrs)	Gender	Summary
4482604-3	8	Male	Disinhibition, physical aggression, abnormal behavior after 1 day Concerta. Concerta discontinued, events resolved
4315723-2	7	Male	Hallucinations, anxiety, sleep disorder after about 1 ½ weeks Concerta. Concerta discontinued, events resolved
4332569-x	6	?	Hallucinations during Concerta. Onset and outcome unknown
4509680-3	5	Male	Aggression and suicide attempt after 1 day Concerta. Concerta discontinued, events ongoing
4377851-5	14	Male	Intentional self-injury and suicidal ideation after about 6 months Concerta. Concerta ongoing, event outcome unknown
4526725-5	15	Male	Suicidal ideation, anorexia, abdominal pain less than 8 months after starting Concerta. Concerta dosage increased and patient become "high" and aggressive. Concerta discontinued. After 5 months, Concerta restarted and "symptoms" (unspecified) recurred.
4327846-2	10	Male	Hallucination, diplopia, headache with one dose Concerta. Concerta discontinued, events resolved. After rechallenge with 1 dose Concerta, chest pain and back pain. Concerta discontinued, events resolved
4385130-5	9	Male	Depression and suicide attempt after 1 week Concerta. Changed to Ritalin and events improved
4471609-4	8	Female	Paralyzing anxiety, anorexia, trembling, severe headache, psychomotor slowdown, nightmares, insomnia, abdominal and chest pain after 3 days Concerta. Changed to Ritalin and events resolved except for slight trembling
4258940-2	11	Male	Panic attack after 2 days Concerta. Concerta discontinued, event resolved
4295943-6	7	Male	Mania and psychosis during Concerta. Concerta discontinued, events resolved

Neurological Adverse Events (N=16)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4258081-4	10	Female	Disorientation, visual disturbance, shaking, aching extremities day of dosage increase after 6 months Concerta. Concerta discontinued, events resolved
4496410-7	11	Male	Dystonia, increased heart rate, tremor hours after dosage increased. Treated with Benadryl and Diastat rectal, events resolved.
4516224-9	12	Male	Seizures (per consumer) after 5 months Concerta. Concerta discontinued, events resolved
4516219-5	14	Male	Seizure-like activity and stress symptoms. Onset and outcome unknown
4443825-9	15	Male	Epilepsy. Onset unknown. Concerta and risperidone discontinued, events ongoing
4290182-7	10	Male	Seizures 2 weeks after increased Concerta dosage. Concerta discontinued, treated with Trileptal, events resolved
4415346-0	10	Male	Seizure with Concerta and sertraline. Onset and outcome unknown
4336843-2	8	Female	Tics with methylphenidate. Onset and outcome unknown.
4516211-0	6	Male	Seizure after 5 months Concerta. Concerta discontinued, event resolved
4531859-5	13	Male	Leg numbness, abdominal pain, asthenia, sleep disorder, tic with Concerta. Concerta dosage decreased, leg numbness resolved. Other events ongoing. Onset unknown
4356824-2	11	Male	Dyskinesia aggravated after 4-6 weeks Concerta. Concerta discontinued, event outcome unknown
4254304-6	11	Male	Focal epilepsy, confusion, restlessness, retrograde amnesia, trembling, sleep walking, eye pain with Concerta. Concerta discontinued, eye pain, focal epilepsy, amnesia ongoing. Onset unknown
4280661-0	14	Male	Absence and tonic-clonic convulsions after 9 months Concerta. Concerta discontinued, events resolved
4458045-1	9	Male	Headache, fever after 2 days Concerta. Concerta discontinued, events resolved
4280109-6	7	Male	Decreased consciousness, increased heart rate after 2nd dose Concerta. Concerta discontinued, events resolved
4486839-5	10	Male	Brain tumor and cyst after 2 years, 4 months Concerta. Concerta discontinued, surgery performed, events resolved. Concerta restarted

Special Senses Adverse Events (N=7)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4318196-9	7	Female	Increased intraocular pressure after 1 year, 2 months Concerta. Concerta discontinued, event resolved
4400046-3	13	Male	Strabismus, diplopia after 1 ½ years Concerta. Concerta discontinued, events improve
4393566-1	15	Female	Abnormal eye movements with Concerta, risperidone, topiramate. Onset and outcome unknown
4381800-3	11	Male	Transient blindness in one eye, ongoing loss of color vision in same eye after 11 months Concerta. Concerta and event ongoing
4284709-9	8	Female	Loss of vision and coloboma in one eye after 1 week Concerta. Concerta ongoing, coloboma recovering, loss of vision outcome unknown
4396478-2	8	Female	Retinopathy after 2-3 months Concerta. Concerta discontinued, event ongoing
4355363-2	10	Male	Loss of function in one ear labyrinth causing vertigo, nausea, nystagmus, with Concerta. Concerta discontinued, event resolved
Cardiovascular Adverse Events (N=20)			
4334745-9	7	Male	"Extremely" high blood pressure, headache with Concerta. Concerta discontinued, events resolved. Onset unknown
4302144-1	9	Female	Hypertension (148/98) after 5 ½ months Concerta. Concerta discontinued, event resolved
4360268-7	12	Female	Increased blood pressure (135/92) with Concerta. Onset and outcome unknown
4333345-4	14	Male	Tachycardia (154 bpm), syncope after one dose of both Concerta and sertraline. Both drugs discontinued, treated with lorazepam, event resolved
4394264-0	11	Male	Increased blood pressure (130/90), dizziness, chest pain, left atrial enlargement per EKG after 4-5 months Concerta. History of heart murmur. Concerta discontinued, events resolved. Concerta restarted, no recurrence at 9 days follow-up
4334746-0	10	Male	Increased blood pressure, headache, dizziness with Concerta. Concerta discontinued, events resolved. Onset unknown

ISR#	Age (yrs)	Gender	Summary
4322060-9	9	Female	Increased heart rate (100-110 bpm), rash, urinary incontinence, insomnia with Concerta. Concerta ongoing, events ongoing except rash. Rash improved with topical treatment
4320336-2	15	Male	Tachycardia (90 bpm) and exertional dyspnea with Concerta. Treated with beta-blocker. Onset and outcome unknown
4392692-0	13	Male	Tachycardia (140 bpm) with Concerta. Concerta dosage decreased, event ongoing. Onset unknown
4369041-7	11	Male	Tachycardia, chest pain, dyspnea on exertion after 3-4 months Concerta. Concerta discontinued, events resolved
4511955-9	11	Male	Chest pain after less than 1 month Concerta. Concerta discontinued, event resolved
4400039-6	16	Male	Chest pain, vomiting, sweating, dyspnea, normal EKG with Concerta. Concerta discontinued, event resolved. Onset unknown
4502929-2	6	Male	Chest pain, headache, unspecified abnormal EKG after less than 1 month Concerta. Concerta discontinued, event outcome unknown
4356830-8	10	Male	Chest pain, dyspnea after 1 year, 4 months Concerta. Event resolved, Concerta discontinued 3 weeks later
4374198-8	16	Female	Syncope after 7 months Concerta while working in hot conditions. Tested positive for PCP although denied use. Concerta ongoing, event outcome unknown
4511328-9	13	Male	Supraventricular extrasystoles found on EKG while hospitalized for concussion during Concerta. Concerta and events ongoing. Onset unknown
4268596-0	11	Male	Chest pain, tachycardia, increased QT interval with Concerta. Onset and outcome unknown
4521840-4	14	Male	Cardiac arrhythmia, AV block, increased QT interval after more than 1 year Concerta. Concerta discontinued, arrhythmia resolved, EKG changes improved. Concerta restarted with beta-blocker and events not recur
4338461-9	11	Female	Peripheral vascular obstruction with cyanosis in toes after about 6 months Concerta. Hospitalized in vascular surgery ward. Treatment and outcome unknown
4453417-3	9	Male	Peripheral vasoconstriction while swimming after 2 years Concerta. Outcome unknown

Cerebrovascular Adverse Events (N=2)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4289271-2	9	Male	Cerebral aneurysm with Concerta. Onset and outcome unknown
4539783-9	7	Male	Cerebrovascular disorder, hallucinations with Concerta. Onset and outcome unknown
Hematologic Adverse Events (N=10)			
4389486-9	13	Male	Henoch-Schönlein purpura after 2 months Concerta. Concerta discontinued, patient treated, event ongoing
4332568-8	13	Male	Iron deficiency anemia after 10 months Concerta. Concerta discontinued, iron supplemented, event outcome unknown
4496194-2	16	Male	Neutropenia with Concerta use. Onset and outcome unknown
4323757-7	14	Male	Thrombocytopenia, hematoma, petechia after 4 ½ months Concerta. Concerta discontinued, steroid treatment, events improve then recur. Events ongoing at 2 months
4453449-5	14	Male	Lymphocytosis, granulocytopenia after one month Concerta. Outcome unknown
4323753-x	10	Male	Eosinophilia with Concerta. Onset and outcome unknown
4531858-3	10	Male	Leukocytosis, thrombocytopenia with Concerta. Onset and outcome unknown
4338462-0	9	Male	Eosinophilia, increased AST after less than 6 months Concerta. Concerta discontinued, event outcome unknown
4509681-5	9	Male	Eosinophilia with Concerta. Onset and outcome unknown
4274303-8	8	Male	Neutropenia, leucopenia, headache after less than 1 month Concerta. Concerta discontinued, events resolved

Gastrointestinal Adverse Events (N=11)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4336343-x	16	Male	Esophagitis after 9 months Concerta. Concerta ongoing, event treated with famotidine and resolved
4301978-7	10	Female	Gallstones, lack of weight gain, anorexia, insomnia after 2 years, 9 months Concerta. Concerta ongoing, cholecystectomy. Gallstones resolved, other events ongoing
4359472-3	10	Male	Acute cholecystitis with Concerta. Onset and outcome unknown
4440673-0	10	Male	Anorexia, drowsiness with Concerta and atomoxetine. Concerta discontinued, anorexia resolved. Onset unknown
4516207-9	8	Male	Stomach ache, anorexia, decreased weight after 1 week Concerta. Concerta discontinued, events resolved
4414598-0	12	Male	Anorexia and decreased weight after less than 5 months Concerta. Concerta continued, events resolved.
4413987-8	11	Male	Appendicitis, anorexia, decreased weight, gynecomastia, insomnia after about 4 years Concerta. Concerta continued, appendectomy performed. Event outcomes unknown
4365919-9	10	Male	Diarrhea with blood and mucus after 2 weeks Concerta. Concerta discontinued, events resolved
4280110-2	9	Male	Increased liver function tests (GGT 184 U/L [nml <19], LDH 306 U/L [nml<300]), weakness after 7 months Concerta. Concerta discontinued, events improved then worsened 2 months later
4418089-2	9	Male	Hepatitis after 1 year Concerta. Concerta discontinued, event resolved
4301422-x	14	Male	Hepatitis after 1 ½ years Concerta. Concerta discontinued, event continuing 3 ½ weeks later
Thyroid Adverse Events (N=1)			
4248765-6	10	Female	Hyperthyroidism after about 4 months Concerta. Concerta and event ongoing

Miscellaneous Adverse Events (N=7)			
ISR#	**Age (yrs)**	**Gender**	**Summary**
4456977-1	10	Female	Malignant hypertension, acute pulmonary edema, bradycardia, multifocal ventricular tachycardia immediately after administration of intranasal phenylephrine during general anesthesia and after over 3 years Concerta. Concerta discontinued, event treated and resolved. Drug interaction questioned
4249345-9	14	Male	Erythematous rash, peripheral swelling, fever after about 1 month Concerta. Concerta discontinued, rash recurred 2-3 more times
4294240-2	15	Male	Acute renal failure after 2 years Concerta. Concerta continued, event treated and resolved
4519995-0	15	Male	Growth retardation after 4 years Concerta. Concerta and event ongoing
4469710-4	8	Male	Hypoglycemia in patient with Diabetes Mellitus during Concerta therapy. Outcome unknown
4333773-7	15	Female	Pregnancy and spontaneous abortion during Concerta therapy. Concerta ongoing
4395758-4	10	Male	Increased incidence of herpetic eye infections "soon" after Concerta dosage increase. Outcome unknown

Attachment 3: Cases in which no adverse event was reported (N=8)[3]

ISR#	Age (yrs)	Gender	Summary
4483855-4	11	Female	Wrong medication dispensed, not ingested
4483854-2	16	Female	Wrong medication dispensed, not ingested
4385322-5	10	Male	Wrong medication dispensed, not ingested
4363194-2	16	Male	Extracted, dried, and snorted contents of one OROS Concerta tablet with no adverse effects. Prescription belonged to a classmate
4386271-9	13	Male	Accidentally ingested two Concerta doses same day with no adverse effects
4517848-5	4	Male	Accidentally ingested three Concerta doses at one time with no adverse effects
4506523-9	14	Male	Ingested four Concerta doses same day because "a lot helps a lot" per patient. No adverse effects
4315325-8	10	Male	Report states only that Concerta was used for 4 months and "discontinued because of side effects"

[3] NOTE: These cases were excluded from the case series.

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/s/

Kathleen Phelan
6/15/05 05:00:49 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
6/15/05 05:10:27 PM
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